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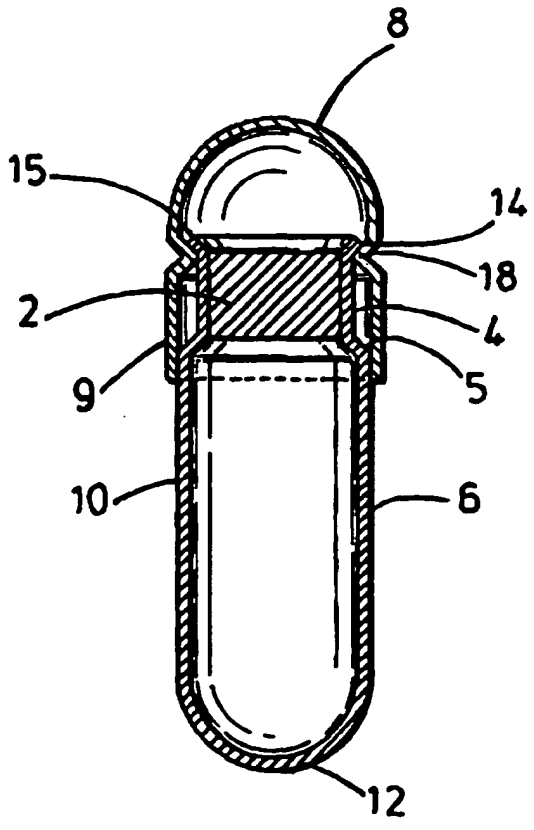
(54) Title: HYDROPHILIC CONTROLLED RELEASE DEVICE

(57) Abstract

A capsule body (6) for a controlled release device has a coating of a hydrophilic material at least inside the neck region (4) adjacent the opening (15). The hydrophilic material may be a film forming material and/or a surfactant. Its purpose is to facilitate ingress of water into the capsule body in order to release a pharmaceutical material contained therein, once the hydrogel plug (2) has swollen and become disengaged from the body after a predetermined time interval. A preferred hydrophilic coating is formed of a mixture of ethyl cellulose and sodium docusate.



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HYDROPHILIC CONTROLLED RELEASE DEVICE

Technical Field

The present invention relates to controlled release devices intended for containing an active material (especially a pharmaceutically active material) which are arranged to release the active material after a predetermined time interval.

Background

International Patent specification W090/09168 discloses a controlled release device of this type which comprises a water-swellable male plug engaged within a female body. A pharmaceutically active material is contained within the device, which may be in the form of capsule. When the capsule is exposed to water, the male plug which is typically formed of a hydrogel material swells and eventually disengages itself from the female body; thereby allowing the pharmaceutically active material contained within the capsule to be released. It has been found that the time taken to disengage the hydrogel plug and so open the device is predictable and reproducible, so that the device may be used to release pharmaceutically active materials within the body of a patient after a predetermined time interval, which is typically in the

range 0.5 to 12 hours. This may, for example, be useful in the treatment of medical conditions where it is desirable to administer a pharmaceutically active material to the patient sometime through the night, while the patient is asleep, so as to provide a desired level of the active material in the patient at a time during the night or when he awakes. It may also be useful to allow dosing of materials at a predetermined point as the capsule passes through the gastro-intestinal tract, for example in the colon.

Patent specification WO92/13521 (Alza Corporation) describes fluid-imbibing dispensing devices for delayed delivery of an active agent, which include an expansion means which absorbs fluid from a surrounding environment. The dispensing device comprises a housing having first and second wall sections telescopically engaged with each other, particularly a capsule having a hollow cap and a hollow body. Either the cap or the body is in the form of a male section fitted inside the open end of the other female section. The expansion means is contained within the device and expands as it absorbs fluid, forcing apart the two sections of the device so as to open the device. The expansion means may be a swellable polymer or an osmotic formulation which swells as it absorbs fluid. In order to allow fluid to come into contact with the expansion means contained within the device, one of the wall sections

adjacent to the expansion means is fluid-permeable. After the sections are disengaged, fluid enters the device and comes into contact with the active agent contained within the device, thereby dispensing the active agent into the fluid.

In order for the pharmaceutically active material to be effectively released from the controlled release device, two things must occur. Firstly, the device must become opened by detachment of the male and female sections so as to enable the entry of liquid. Secondly, liquid must in fact enter the device so as to enable the pharmaceutically active material to be flushed out of the device into the surrounding liquid. Since the objective is to enable the patient to be dosed with the pharmaceutically active material at a chosen time, both these steps must occur. The present invention is particularly concerned with the second step, that is to say with ensuring that an effective release of material occurs, following opening of the controlled release device.

A particular application of the controlled release device is release of pharmaceutically active material into the colon. In the colon portion of the gastro-intestinal tract, the waste material contained therein has a particularly high solids content and a particularly low water content. This exacerbates the problem of effectively releasing the contents of the controlled release device into the surrounding fluid

s that it bec mes available for absorbtion into the patient's system. The relatively low water content means that a minimal amount of water is available for flushing or dissolving the pharmaceutically active material from within the controlled release device. Furthermore, the high solids content means that there is a relatively low degree of agitation within the colon, so that there is a reduced likelihood of the contents of the controlled release device being expelled by movement of the device within the gastro-intestinal tract.

It is an object of the present invention to address the problem of efficient release of material from the body of a controlled release device.

Summary of the Invention

The present invention provides a water-impermeable body for a controlled release device for containing a material to be released when the body is immersed in an aqueous liquid, the body having an opening through which the material is released from the body, the interior surface of the body at least in a region thereof adjacent the opening comprising a hydrophilic material.

Thus, generally speaking, the present invention resides in coating or otherwise providing at least a portion of the interior surface of the body adjacent the opening with a hydr philic material which

facilitates ingress of aqueous liquid from the surroundings. Generally speaking, the material to be released from the controlled release device is a powdered material or other solid material which is inevitably filled into the body together with a quantity of air. This may be equally true when liquid fillings are provided within the controlled release device. The present inventors have observed that when the body becomes opened by release of the male and female sections of the device, there is a tendency for an air bubble to form within the area of the opening, and this air bubble inhibits ingress of aqueous liquid into the capsule body. The present inventors have successfully addressed this problem by coating the interior surface adjacent the opening in the body, which is the area in which the air bubble or bubbles normally collect, with a hydrophilic material. The hydrophilic material is normally present as a coating, but may if necessary be formed as an intrinsic part of the material from which the body is formed. It is believed that the provision of the hydrophilic material helps release the air bubble from its position obstructing the opening to the body. Release of the air bubble may be facilitated by a change in the surface energy of attraction of the air for the interior surface of the body, or more likely by promoting the wetting of the interior surface of the body by aqueous liquid and thus promoting the flow of

aqueous liquid into th body and thereby forcing the air bubble out. However, the present inventors do not wish to be limited by any particular theory of operation. As will be demonstrated herein, the provision of a hydrophilic surface in this way is particularly effective in removing the air bubble from the opening of the body of the controlled release device.

Preferably, the body is in the form of a capsule body prepared by conventional capsule forming techniques, which generally involve dipping a mould pin in a solution of the material (such as gelatin) from which the capsule is to be formed. Spraying could be used instead of dipping. The gelatin is then dried and stripped from the pin. The capsule body may then be trimmed as necessary. Alternatively, the capsule body might be made by other known manufacturing techniques, such as injection moulding of thermoplastic materials.

The water-impermeable wall of the body intended to contain the active material may be formed from a wide variety of materials. The wall of the body is impermeable to water (and generally also insoluble in water) such that aqueous liquid cannot enter the body until the body has opened after the predetermined time interval. By "water-impermeable" we mean that substantially no water passes through th coating during the normal period in which th body is in

c ntact with aqueous liquid up to opening of the controlled release device. The wall of the body may be of homogenous construction or may be laminated. Examples of materials suitable for use in the construction of the body include polyethylene, polypropylene, poly(methylmethacrylate), polyvinylchloride, polystyrene, polyurethanes, polytetrafluoroethylene, nylons, polyformaldehydes, polyesters, cellulose acetate and nitrocellulose.

However, a preferred construction uses a water-impermeable coating to cover the exterior of a body which has been formed from a water-soluble material since this may be conveniently made using conventional technology. The coating may formed by dipping the body in a solution of a material which forms a layer which is impermeable to water. Alternatively, the body might be spray coated. A preferred class of capsule bodies are conventional hard gelatin or starch capsule bodies coated with a solution of polyvinylchloride, a polyvinyl acetate copolymer or an ethyl cellulose solution and dried to form a water-impermeable coating.

In a particularly preferred embodiment of the present invention, the body is a female body which comprises a male member engaged within the opening. In particular the male member may be a plug provided within a neck p rtion of the body adjacent the opening thereof. The plug is usually of substantially

cylindrical configuration and may be formed of a water-swellable material, preferably a hydrogel. As it absorbs water, the hydrogel plug swells and becomes disengaged from the female body. The hydrogel is preferably a water-swellable material as disclosed in patent specification W090/09168. Usually, the neck portion is substantially cylindrical, so as to form a tight fit with the cylindrical male plug.

In another embodiment, the male member is a hollow member closed at one end, whose opposite open end engages within the neck of the female body. A water-swellable material is provided within the controlled release device which serves to disengage the female body after a pre-determined time, by forcing the male member and the female body apart as the material swells in the presence of water. The swellable material inside the controlled release device may be an osmagent or an osmopolymer. Such an arrangement is disclosed in patent specification W092/13521. In order to allow water to enter the controlled release device and to contact the water-swellable material a portion of the wall of the device adjacent thereto is preferably semi-permeable, that is to say it is permeable to the passage of water into the device but impermeable to release of other substances from within the device.

Th efficient removal of air bubble(s) from the opening to the body according to the invention

requires that the interior surface of the body in the region adjacent the opening be of a hydrophilic material. The body itself may be formed from a suitable hydrophilic material, but generally speaking the choice of suitable materials is limited, since hydrophilic materials tend to be water soluble and run the risk of allowing water to enter through the wall of the capsule body prior to opening of the device. The body is more usually formed of a material which is water-insoluble or which has been coated with a water-insoluble coating. Such water-insoluble materials by their nature terd not to be hydrophilic. Therefore, in a preferred embodiment of the present invention, the hydrophilic material is provided as a coating. The coating may be provided in any suitable manner, such as by dip coating or spray-coating. Where spray coating is employed, it is found that sufficient of the hydrophilic coating material becomes sprayed through the opening of the body to effectively coat the region of the interior surface of the body immediately adjacent to the opening, where there is a likelihood of air bubble lodgement. It is not generally speaking necessary that the whole of the interior surface of the body be coated with the hydrophilic material.

The hydrophilic material may generally be applied by application of a solution or suspension of the hydrophilic material in a suitable aqueous or organic

liquid vehicle.

Generally speaking, the coating should be a smooth coherent coating which is non-tacky, so that the normal flow characteristics of the controlled release devices, (e.g. capsules), are unimpaired and clumping does not occur. The material should generally dry to a solid coating.

The hydrophilic material may comprise a suitable surfactant material provided that it fulfils the criteria set out above. Also, film forming materials of a hydrophilic nature may be used and a multitude of such materials are known in the art. The film forming material may be insoluble in water or may have water solubility. Other things being equal, water soluble coatings tend to exhibit relatively good emptying properties. Finally, mixtures of film forming materials and surfactants may be employed, and these have been found to be particularly useful in enhancing the hydrophilic properties of the film former.

Suitable film forming materials of varying hydrophilicity include celluloses, polyacrylates, polymethacrylates, polyacrylamides, polyvinyl alcohols, and polyvinylpyrrolidones. Specific film forming materials include hydroxypropyl methyl cellulose, methyl cellulose, hydroxypropyl cellulose, ethyl cellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, acrylic resins such as

Eudragits (trade mark), hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate, zein, shellac, cellulose acetate and cellulose triacetate. There are also a number of suitable sugar-based coating materials, such as sugar, gelatin, acacia gum and starch.

Suitable surfactants for inclusion in the hydrophilic coating include anionic, nonionic and cationic surfactants. Typical examples include sodium lauryl sulphate, sodium docusate, sodium oleate, castor oils, hydrogenated castor oils, fatty acid esters, and fatty acid alcohols (e.g. cetyl and lauryl). The surfactant may also be a polyoxyethylene or derivative thereof, such as polyoxyethylene sorbitan monolaurate (e.g. Tweens), polyoxyethylene sorbitan monooleate (e.g. Spans), fatty acid ethoxylates such as polyoxyethylene stearate, alcohol ethoxylates such as polyoxyethylene oleylether, polyoxyethylene-polyoxypropylene copolymers, and polyethylene glycols. Span and Tween are trade marks.

A particularly preferred embodiment of the present invention employs a conventional hard gelatin capsule body which has been coated with ethyl cellulose to make it water insoluble. In order to provide a hydrophilic coating according to the present invention, the capsule body is spray coated with a further coating of hydroxypropylmethyl cellulose (HPMC). Alternatively, gelatin may be used as the

hydrophilic coating ov r the water insoluble capsule body, in order to give the capsule a familiar appearance and feel to a patient.

The hydrophilic coating generally comprises from 0.1 to 50% by weight of the body of the controlled release device, particularly 1 to 20% by weight, especially 2 to 10% by weight.

The hydrophilic nature of the hydrophilic material may be quantified in terms of the advancing contact angle of the material (which may be measured using the standard Wilhelmy plate technique), which reflects the surface activity of the material. Preferably, the advancing contact angle is less than 80°, preferably less than 75°, and advantageously less than 70°. It may lie in the range of 50 to 75°, particularly 60 to 70°. The HLB (hydrophilic lipophilic balance) value for a surfactant hydrophilic material is generally greater than 10, usually greater than 20, and preferably greater than 30. The HLB value may lie in the range 25 to 55, preferably 30 to 50.

Whilst the present invention has been discussed with reference to the release of a pharmaceutically active material, in principle it may equally well be applied to the timed release of other non-pharmaceutical materials.

Detailed Description of Preferred Embodiments

Embodiments of the present invention will now be described by way of example only.

In the Figures, Figure 1 is a cross-sectional elevation of a controlled release device in the form of a capsule consisting of a body, hydrogel plug and cap.

The capsule is more particularly described in our published patent specification W094/09745, and comprises a male member in the form of a plug 2 formed of a hydrogel material, inserted in neck 4 of female body 6. The capsule is closed with a cap 8. The body 6 is, for example, of overall length about 18mm and comprises a cylindrical main portion 10 and closed end 12. The main body narrows to the neck portion 4 at a shoulder region 5. The neck portion is substantially cylindrical (internal diameter when coated is about 6.7mm) so as to receive the male plug 2 with a close tolerance. The neck portion then flares out to a flared mouth portion 14 which has an opening 15 of a diameter substantially the same as the diameter of the main body portion 10.

The male plug 2 is formed of a hydrogel material (such as disclosed in W090/09168) and is usually inserted so that the upper end of the plug is above, level with or below the upper end of the capsule body.

The capsule is then sealed with the cap 8 which is provided with detents 18 which clip under the rim

of the flared mouth portion thereby locking the cap in place.

The cap has a cylindrical skirt portion 9 which extends down to the open end of the cap. The lower end of the skirt portion extends downwardly past the shoulder 5 of the body and encloses an upper part of the body with only a small clearance. This helps to stabilise the cap and prevent it tilting from side to side. It also allows the cap to be sealed to the body by means of an annular band passing over the junction therebetween.

EXAMPLE 1. (Production of Hydrogel Plug)

Hydrogel rods were prepared by polymerising 6,000 grams of polyethylene glycol PEG 8000 (Pharma) of number molecular weight Mn 8700 and ratio Mw/Mn = 1.03 (where Mw is the mean molecular weight) with 111.04 grams of hexanetriol, 506.8 grams of Desmodur W (dicyclohexylmethane-4, 4-diisocyanate), and catalysed by 0.6 grams of anhydrous ferric chloride. The mole ratios were PEG 8000 (1 mole), hexanetriol (1.2 moles), Desmodur W (2.3 moles) and ferric chloride (0.01% by weight of PEG). The PEG 8000 was melted and dried to less than 0.05% w/w moisture content in a Buchi Rotavapor at 95°C, at a pressure less than 5 millibars for a period of two hours. Then, the ferric chloride was dissolved in the hexanetriol at 75°C, and the mixture stirred into the dried PEG for 5 minutes

at 100 rpm. The mixture at 85°C was then mixed with the Desmodur W by pumping into a mixer rotating at 1500 revolutions per minute. Molten polymer at about 80°C was then dispensed into tubular polytetrafluoroethylene moulds 25cm long and internal diameter about 6.7mm under a vacuum of less than 50 millibars. Curing took place at 95°C for 4 hours in a fan equipped oven. The hydrogel polymer rods were then allowed to cool.

The hydrogel rods were washed by immersion in a circulating stream of water containing butylated hydroxy anisole (BHA) as a stabiliser.

The washing removed water-soluble extractable substance from the polymer and the BHA stabiliser becomes incorporated into the polymer.

The swelling factor is defined as (Ws-Wd)/Wd x 100, where Ws is the swollen weight and Wd is the dry weight. The hydrogels were found to have a swelling factor of 270± 25.

The hydrogel rod was then cut into plugs, each generally of a nominal length 4mm.

EXAMPLE 2 (ethyl cellulose coating)

A gelatin capsule body as shown in Figure 1 was coated with a water-insoluble water-impermeable ethyl cellulose coating in the following manner. A batch of gelatin capsule bodies were introduced into an Accelacota spray coating machine (Manesty Machines

Ltd., U.K.). The spray coating machine was operated according to the manufacturer's instructions. A solution of ethyl cellulose (E100) in a mixture of isopropyl alcohol and acetone (50:50 by wt.) was sprayed onto the capsule bcdies until an ethyl cellulose coating representing an 80% weight gain had been deposited. The inlet air temperature to the coating machine was 45°C and the outlet air temperature 40°C. The drum speed was 9.5rpm. The ethyl cellulose coated gelatin bodies were then stored for future use. The ethyl cellulose coating covers the entire outer surface of the capsule body and extends part way down the interior surface of the capsule body, so that all regions of the body which in use are in contact with aqueous liquid when the hydrogel plug is installed, are coated with the water impermeable ethyl cellulose coating.

EXAMPLE 3 (Coating of ethylcellulose coated gelatin bodies with an additional topcoat of hydrophilic material)

The problem of poor emptying from ethylcellulose coated gelatin bodies has been observed. Described here are the various processing conditions and coating solution formulations used to obtain the various batches of hydrophilic capsule bodies subsequently tested for air bubble formation and tablet emptying time.

PROCEDURE

50g of ethylcellulose coated bodies produced according to Example 1 were added to a coating machine of the type given below and heated for 10 minutes prior to spray application of the coating solution. Spraying was continued until the required weight loading was achieved.

The Table below shows the equipment used, together with the process conditions recorded, for each batch of coated bodies investigated in the determination of emptying rate and air bubble formation studies.

BATCH	PROCESS CONDS.	SOLN. FORMULA	WT. GAIN
P09394	Inlet air temp 45°C Atomising air 1.0bar	sodium lauryl, sulphate 0.54g acetone 15ml IPA 15ml water to 40ml	1%
D195136	Inlet air temp 45°C Drying temp 35°C Atomising air 1.0bar Nozzle size 0.8mm	HPMC 30g water to 500ml	14%
D195130	AS ABOVE		2.5%
D195133A	Inlet air temp 45°C Drying temp 35°C Atomising air 1.0bar Nozzle size 0.8mm	sodium lauryl, sulphate 2g HPMC 12g water to 200ml	14%
D195133B	AS ABOVE		2.5%
D195155B	Inlet air temp 35°C Outlet air temp 25°C Atomising air 1.0bar Nozzle size 1.0mm Drum speed 24rpm	acetone 830ml ethylcellulose 42.5g diethylphthalate 2.5g Na docusate 16.6g IPA to 1660ml	16%

All batches were spray coated using a Strea 1 coating machine (Niro/Atomiser, Switzerland) except for the last batch D195155B which was coated using a Hicoater machine (from Freund, Germany). The coating machines were operated according to the manufacturer's instructions. IPA is an abbreviation for isopropyl alcohol. HPMC is an abbreviation for hydroxypropylmethyl cellulose.

Each batch of bodies, following coating, was stored in an appropriate labelled container prior to commencement of the following experiments.

EXAMPLE 4 (Effect of various hydrophilic coatings and wetting agents on air bubble formation)

The incorporation of a wetting agent and/or hydrophilic film layer onto an ethylcellulose (E100) coated gelatin capsule body, as a topcoat was investigated. The occurrence of air bubbles upon plug ejection was noted as was the subsequent contents emptying. The experiment was recorded on time lapse video to allow more complete analysis.

PROCEDURE

10 capsule bodies from each of the following batches were filled:

BATCH NO.	COATING
A75DEV008	ethylcellulose
D195136	ethylcellulose with additional 14% weight gain HPMC
D195133A	ethylcellulose with additional 14% weight gain of a mixture of HPMC and 16.5% sodium lauryl sulphate
P09394	ethylcellulose with additional 1% weight gain sodium lauryl sulphate
D195133B	ethylcellulose with additional 2.5% weight gain of a mixture of HPMC and 16.5% sodium lauryl sulphate
D195130	ethylcellulose with additional 2.5% weight gain HPMC

Each capsule body was filled with a 200mg slug of Low Substituted Hydroxy Propyl Cellulose (LH21) powder. This material expands in contact with water.

Then each capsule was fitted with a 3.00mm long hydrogel plug produced according to Example 1. It was only possible to video film a maximum of 10 capsules at any one time. Therefore the experiment was repeated until all six coatings had been investigated. Once assembled the devices were placed in a plastic stand and attached to the base of a glass water tank. Water (room temperature) was added to the tank and the video camera set to record. Results were obtained by watching video replays of the experiment.

RESULTS

BATCH NO.	NO.TESTED	NO.WITH AIR BUBBLES	EMPTYING
A75DEV008	15	5	poor from those with air bubbles
D195136	10	0	GOOD
D195133A	10	0	GOOD
P09394	10	0	GOOD
D195133B	10	0	GOOD
D195130	10	0	GOOD

These results suggest that air bubbles only remained in those bodies coated with the ethyl cellulose coating alone.

EXAMPLE 5 (Determination of emptying times of hydrophilic coated capsule bodies)

The results of Example 4 indicated that incorporation of a top layer of hydrophilic material by conventional spray coating techniques decreased

significantly the incidence of air bubble retention upon plug ejection. This experiment aimed to quantify the improvement seen in emptying of the fill material from the capsule body.

PROCEDURE

10 capsules from each of the following batches were taken:

BATCH NO.	COATING
A75DEV008	ethylcellulose
D195136	ethylcellulose with additional 14% weight gain HPMC
D195133A	ethylcellulose with additional 14% weight gain of a mixture of HPMC and 16.5% sodium lauryl sulphate
D195155B	ethylcellulose with additional 16% weight gain of a mixture of ethylcellulose and 16.5% sodium docusate

Each capsule body was filled with 100mg of LH21 powder. This was compacted. A placebo tablet was placed on top. The LH21 powder is intended to expand in contact with water and thereby to eject the tablet from the body. The devices were fitted with a 2.5mm long plug of a hydrogel produced in Example 1 which protruded 1.5mm out of the neck of the body, and gave a conveniently short plug ejection time for direct observation. They were then placed on a plastic holder and fixed onto the base of a glass tank. Water (room temperature) was added. The experiment was

recorded in real time using a video camera and repeated until all 4 coatings had been investigated. The video could be replayed to find the time from plug ejection to tablet emptying for each device. The mean time could then be calculated. The results are set out below.

BATCH NO.	NO. TESTED	MEAN TIME FOR TABLET EMPTYING (sec)
A75DEV008	10	no emptying. All 10 devices formed air bubbles
D195136	10	65
D195133A	8	23
D195155B	8	22

The sodium lauryl sulphate and sodium docusate containing film topcoated capsules emptied very rapidly. Air bubbles were observed inside the body but these dispersed instantaneously upon plug ejection.

In comparison the HPMC topcoated bodies emptied at a slightly slower rate because the air bubbles formed upon plug ejection were dispersed less rapidly.

The ethyl cellulose coated comparison bodies did not empty at all. The ejected plugs remained sitting on the capsule bodies, with air bubbles located in the neck of the body. Even upon physical removal of the plug no tablet emptying was seen.

From this evidence, the provision of a hydrophilic coating such as HPMC with or without

incorporation of a wetting agent such as sodium lauryl sulphate or sodium docusate as a top film layer results in rapid dispersion of the air bubble at the capsule/dissolution media interface, upon hydrogel plug ejection. This allows the expulsion system (in this case LH21 powder) to become wetted and hence enables tablet expulsion. Thus the expedient of hydrophilising the inner top layer of the capsule body according to the invention significantly assists emptying of the contents of the body.

EXAMPLES 6 to 8 (Correlation of Emptying with Hydrophilicity).

Three criteria for selecting surfactant/film top coats were investigated. These are HLB value (where applicable), advancing contact angle measurement and in-vitro emptying performance. All three methods can be combined to predict the best film-surfactant system. Results indicate that two mechanisms may exist which improve emptying.

Firstly, the addition of a surfactant to an insoluble ethylcellulose film and secondly, using a soluble film with or without surfactant.

Good emptying appeared to correlate with a low mean advancing angle. Similarly poor emptying would be indicated by a higher mean advancing angle.

i) For the surfactant/ethylcellulose system best in-vitro emptying results (100% of those tested

emptied) were seen with the anionic surfactant sodium docusate. Advancing contact angle measurement gave a mean advancing angle of 62.3 (compared with 85.2 for ethylcellulose alone). This compares with mean advancing angles of around 75 which were seen for Brij 72 and Synperonic F127 which did not perform well in the in-vitro emptying tests (only 5 and 10% respectively of devices tested emptied).

The third non-ionic surfactant screened (Myrj 53, a fatty-acid ethoxylate) gave a mean advancing angle of 69.9 and also performed significantly better (55% of capsules tested emptied) in the in-vitro emptying test.

The measurement of advancing contact angle correlates well with the HLB values for individual non-ionic surfactants. Results indicate that surfactants with HLB values below 14 gave subsequent mean advancing angles of around 75°. Whereas the mean advancing angle for Myrj 53 (HLB 17.9) was around 70°. HLB values also correlate well with the results for in-vitro emptying performance.

The measurement of advancing contact angle would have predicted that sodium docusate (as an additive to ethylcellulose) would perform best in the in-vitro emptying test.

ii) For soluble films the results are more complex.

Because the mean advancing angle for both HPMC and HPMC/SLS is high we would have predicted poor emptying performance in-vitro. However, results (60% and 70% respectively of capsules tested emptired) show reasonable performance. We speculate that the HPMC is dissolving and this is enhancing water ingress into the capsule body and promoting expulsion system activation and hence improving emptying performance.

Choice of Surfactant

Surfactants are split into 3 main groups:-

1. anionic surfactants
2. cationic surfactants
3. non-ionic surfactants

Of these, anionic, eg sodium lauryl sulphate, and non-ionic, eg alcohol ethoxylates, are most commonly used in pharmaceutical products.

Within these groups hydrophilicity of surfactants varies and they are assigned HLB values accordingly. High HLB values correspond to more hydrophilic materials. In general anionic and cationic surfactants have higher HLB values than non-ionic surfactants.

For this particular investigation two film forming materials, one soluble (HPMC) and one insoluble (ethylcellulose), were chosen, together with two anionic surfactants (sodium lauryl sulphate and sodium docusate) and three non-ionic surfactants (Brij

72, Myrj 53 and Synperonic F127). These materials were chosen because of their pharmaceutical acceptability, however, the results and concept apply equally to non-pharmaceutical materials of similar nature.

Within the non-ionic surfactant group an example of the three main types were chosen, ie Brij 72 (an alcohol ethoxylate ie polyoxyl 2 stearyl ether), Myrj 53 (a fatty-acid ethoxylate ie polyoxy 50 stearate) and Synperonic F127 (a Poloxamer ie a polyoxyethylene polyoxypropylene copolymer).

These three surfactants also gave a range of HLB values (4.9 for Brij 72 to 17.9 for Myrj 53).

The detailed procedures are given in Examples 6 to 8.

EXAMPLE 6 (Top-coating of impermeable bodies with different composition film/surfactants)

Gelatin capsule bodies which had been previously coated with a water-impermeable ethylcellulose coating were top-coated with a hydrophilic coating as follows.

A Strea 1 Aeromatic Aerocoater was used to top-coat the capsule bodies. The following spraying parameters were used for each batch:

Atomising Pressure	1.0 bar
Flow Rate	6rpm
Outlet Temp	35°C
Inlet Temp	40°C
Column Height	22cm
Nozzle Diameter	0.8mm

Table 1 gives the formulation details of each coating solution and the mean weight loading of the applied film.

Table 1

Top-Coat	Formulation Details	Weight if Surfactant in Top-Coat(mg)
ethylcellulose 100/sodium docusate	5.7g ethylcellulose 100, 0.3g diethylphthalate, 2.0g docusate sodium, acetone:IPA(50:50) to 200ml	1.4
HPMC	12.0g Pharmacoat 606, distilled water to 200ml	0
HPMC/sodium lauryl sulphate	12.0g Pharmacoat 606, 2.0g sodium lauryl sulphate, distilled water to 200ml	1.0
ethylcellulose 100/Brij 72	5.7g ethylcellulose 100, 0.3g diethylphthalate 2.0g Brij 72 acetone:IPA(50:50) to 200ml	1.4
ethylcellulose 100/Myrj 53	5.74g ethylcellulose 100, 0.3g diethylphthalate, 2.0g Myrj 53, acetone:IPA(50:50) to 200ml	1.3
ethylcellulose 100/Synperonic F127	5.7g ethycellulose 100, 0.3g diethylphthalate, 2.0g Synperonic F127, acetone:IPA(50:50) to 200ml	1.3

Upon achieving an approximate mean weight loading of 5.5mg the bodies were removed and tested for in-vitro emptying performance. (IPA is an abbreviation for isopropyl alcohol).

EXAMPLE 7 (In-Vitro emptying performance of top-coated capsule bodies)

The following in-vitro test was used to help evaluate different top-coats. In the test the orientation of the capsule is important. After plug ejection, vertical capsules always showed very poor emptying due to the presence of an air bubble in the neck. Vertical position was therefore adopted to provide maximum challenge.

Procedure

20 top-coated bodies from each batch were then taken and filled with 100mg of Low Substituted Hydroxy Propyl Cellulose (LH21) and a placebo tablet. Each capsule body had a short 1.6mm (approximate) hydrogel plug inserted in the neck to the same depth. The capsules were then placed in a water bath filled with distilled water at 37°C (± 2°C). A video camera was set up to record what happened upon detachment of the hydrogel plug. The video tape was replayed back at a later date and the number of bodies which had emptied was noted. Emptying was taken to be expulsion of the placebo tablet from the top of the capsule body. The results are given in Table 2.

Table 2

Top-Coat	No Tested	No Fully emptied	% which emptied fully
none, ie ethylcellulose	20	0	0
ethylcellulose docusate sodium	20	20	100
ethylcellulose /Brij 72	20	1	5
ethylcellulose /Myrj 53	20	11	55
ethylcellulose /Synperonic F127	20	2	10
HPMC	20	12	60
HPMC/sodium lauryl sulphate	20	14	70

Each of the top-coats improved emptying over the results seen for the comparison bodies which had no top-coat. Docusate sodium appeared to be most effective at aiding water ingress into the capsule body.

EXAMPLE 8 (Contact angle measurement of films cast from each of the top-coat formulations onto microscope cover-slips.)

The in-vitro emptying experiment of Example 7 gave an indication as to which film/surfactant combination would give suitable performance. HLB (hydrophilic lipophilic balance) values could be used to predict which surfactants were most hydrophilic; however, contact angle measurement gives a numerical

value which would allow us to rank film/surfactant combinations. The measurement of the advancing angle using a contact angle measuring technique provides a better understanding of which film/surfactant combinations were most suitable.

Procedure

Solutions were prepared according to the formulations in Table 1. This time, however, all weights were noted to 4 decimal places and all solutions were made up to volume using volumetric flasks. This ensured that the concentration of surfactant (where appropriate) was the same (1.00% w/v) for each solution.

Five examples of films on cover-slips were prepared from each solution as follows.

The cover-slip was submerged in the solution using tweezers. The solvent was then evaporated by passing warm air over the cover-slip. The process was repeated a further three times to ensure a film was deposited on both sides of the cover-slip. Five examples from each film-type were prepared.

The samples were then analysed for contact angle using water as the liquid medium. The technique used to measure contact angle was a standard Wilhelmy plate technique, using a Cahn DCA apparatus. The plate is suspended from a microbalance and the liquid raised using a motorised platform. The force is recorded as

a function of distance and the contact angle calculated from the force at zero depth of immersion (by an extrapolation procedure). The force measured is a function of surface tension, plate perimeter and contact angle.

The advancing contact angle was used as an appropriate parameter for comparison. The mean of five advancing angles is given in the results Table 3. Table 4 gives values for various surfactants. Figure 2 shows graphically the relationship between contact angle and percent capsule body emptying.

Table 3

Top-Coat	Mean advancing Angle (n=5)	S.D.
ethylcellulose (comparison)	85.2	1.6
HPMC	82.1	4.8
HPMC/sodium lauryl sulphate	78.2	3.3
ethylcellulose/Synperionic F127	75.6	1.6
ethylcellulose/Brij 72	75.9	0.1
ethylcellulose/Myrj 53	69.9	1.1
ethylcellulose/docusate sodium	67.3	1.3
Glass cover slip (control)	54.1	12.5

Table 4

Surfactant	Type	HLB Value	Mean Advancing Contact Angle	% Emptying
sodium docusate	anionic	-40	67.3	100
* sodium lauryl sulphate	anionic	-40	78.2	70
Mryj 53	non-anionic	17.9	69.9	53
Brij 72	non-anionic	4.9	75.9	5
Synperionic	non-anionic	14.0	75.6	10

*when blended with HPMC

The results show that the advancing contact angle for each of the top-coats is lower than that for ethylcellulose alone. This indicates that each of the top-coats improves the ability of water to spread on its surface. This correlates with a quickened ingress of water into the capsule and hence increases the likelihood and speed of product emptying.

Again these results show that a good surfactant to add to ethylcellulose is docusate sodium as it has the lowest measured mean advancing angle.

Thus, the application of a hydrophilic top-coat improves spread of water on the capsule surface and hence promotes expulsion of capsule contents when compared to the standard ethylcellulose only coating.

CLAIMS

1. A water-impermeable body for a controlled release device for containing a material to be released when the body is immersed in an aqueous liquid, the body having an opening through which the material is released from the body, the interior surface of the body at least in a region thereof adjacent the opening comprising a hydrophilic material.

2. A body according to claim 1 wherein the hydrophilic material is provided as a coating on the interior surface of the body.

3. A body according to claim 2 wherein the coating is a spray-coating which covers the exterior surface of the body and the interior surface of the body in a region adjacent the opening.

4. A body according to claim 2 or 3 wherein the hydrophilic coating material includes a surfactant.

5. A body according to claim 4 wherein the surfactant is sodium docusate, sodium lauryl sulphate or sodium oleate.

6. A body according to claim 4 or 5 wherein the surfactant has an HLB value of at least 30.

7. A body according to claim 6 wherein the HLB value is in the range 30 to 50.

8. A body according to any of claims 4 to 7 wherein the surfactant is present admixed with a film forming material.

9. A body according to claim 8 wherein the hydrophilic material comprises a mixture of sodium docusate and ethylcellulose.

10. A body according to claim 2 or 3 wherein the hydrophilic coating material is a hydrophilic film forming material.

11. A body according to claim 10 wherein the film forming material is hydroxypropyl methyl cellulose.

12. A body according to any of claims 10 to 11 wherein the hydrophilic coating material is a mixture of a hydrophilic film-forming material and a surfactant.

13. A body according to any of claims 2 to 12 wherein the hydrophilic coating comprises from 1 to 20% by weight thereof.

14. A body according to any preceding claim wherein the hydrophilic material has an advancing contact angle of less than 75°.

15. A body according to claim 14 wherein the advancing contact angle is in the range of 60 to 70°.

16. A body according to any preceding claim wherein the water-impermeable body is formed of gelatin having a substantially water-impermeable coating thereon.

17. A body according to claim 16 wherein the substantially water-impermeable coating is ethyl cellulose.

18. A body according to any preceding claim in the form of a capsule body.

19. A body according to any preceding claim wherein a plug of a water-swellable material is provided within a neck portion of the body adjacent the opening.

20. A body according to any of claims 1 to 18 wherein a hollow male member is engaged within a neck of the body, and a water-swellable material is provided which serves to disengage the hollow male member as the material swells in the presence of water.

21. A controlled release device which comprises a body according to any preceding claim.

22. A device according to claim 15 which contains a pharmaceutically active material.

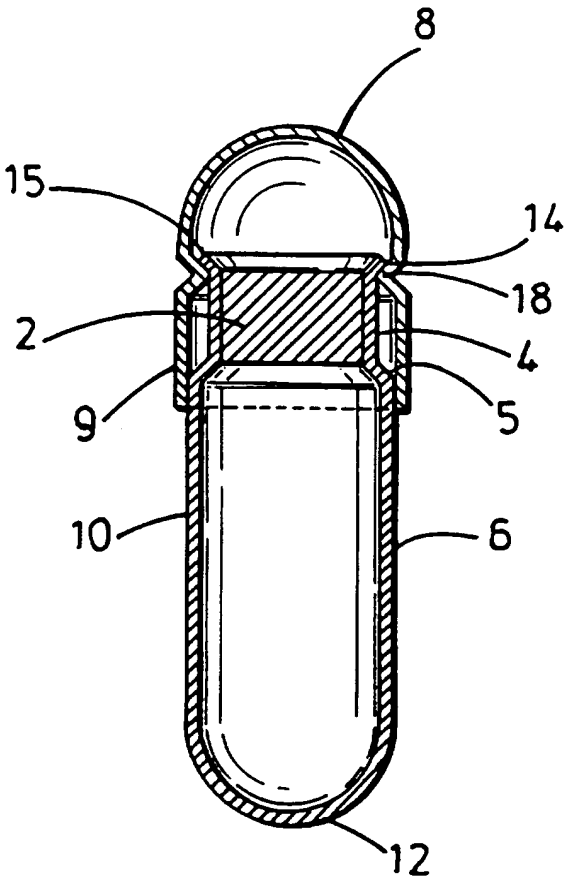

FIG. 1

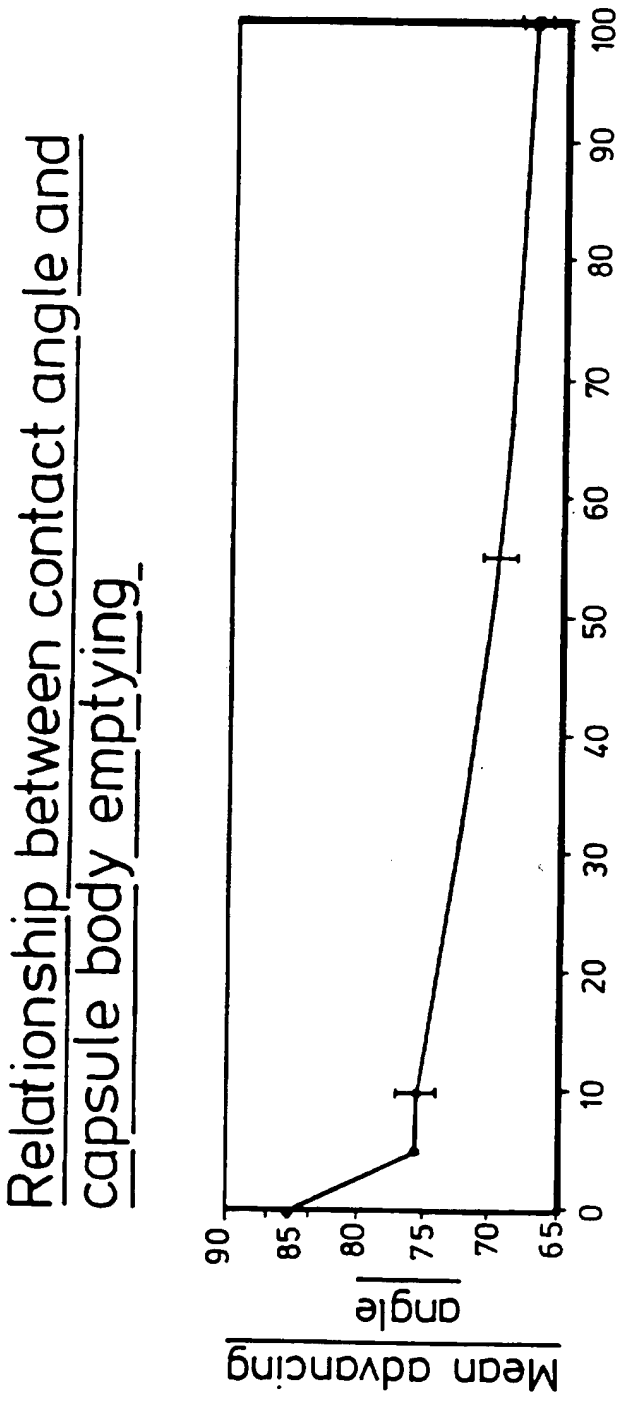
Relationship between contact angle and capsule body emptying
Mean advancing angle
90
85
80
75
70
65
0
10
20
30
40
50
60
70
80
90
100
% emptying

FIG. 2

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/GB 95/01962

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/52 A61J3/07

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,94 09745 (R.P. SCHERER CORPORATION) 11 May 1994 cited in the application see the whole document ---	1-22
A	GB,A,2 243 777 (NATIONAL RESEARCH DEVELOPMENT CORPORATION) 13 November 1991 see page 1, line 24 - page 2, line 27 see page 10, line 24 - page 11, line 6 ---	1-22
A	US,A,4 440 014 (HATTORI ET AL.) 3 April 1984 see column 1, line 54 - line 64 ---	1-22

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 November 1995	12.12.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Benz, K

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INTERNATIONAL SEARCH REPORT

Int'l Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 116 743 (WARNER-LAMBERT COMPANY) 29 August 1984 see page 6, line 32 - line 37 see figure 4 see page 8, line 1 - line 38	1-22

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Inte nal Application No
PCT/GB 95/01962

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